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Chronic Lymphocytic Leukemia: Raising Expectations in the Treatment of Elderly Patients

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Abstract

Many advances have been seen in CLL treatment in recent years, primarily benefitting young, fit patients. However, CLL is primarily a disease of the elderly, and many elderly patients currently receive sub-optimal treatment. This is in part due to a lack of consensus surrounding how best to classify their health status. In order to ensure that elderly patients, whether 'fit' or 'unfit' receive the most appropriate treatment, there is a need for refinement of the screening tools currently used, and furthermore, a need for standardization.

Treatment regimens such as FCR, currently considered the standard of care for CLL treatment, often cannot be recommended for elderly patients who are frequently ineligible for fludarabine-based therapy due to co-morbidities. Several targeted 'chemotherapy-free' treatments are being investigated for use in these patients. Additionally, less toxic chemotherapy regimens are under investigation, including chlorambucil and bendamustine, both in combination with the anti-CD20 antibodies rituximab and, more recently, obinutuzumab. Early results have been promising, and suggest the possibility of improved outcomes in this patient group who, actually, represent the majority of those with CLL.

Keywords: Chronic lymphocytic leukemia; Elderly; Unfit; Bendamustine; Chlorambucil; Fludarabine; Rituximab

Introduction

Recent years have seen substantial progress in our understanding of the biology of chronic lymphocytic leukemia [CLL], particularly with regard to the detection of molecular prognostic factors and the development of more effective therapies. However, many of the milestone studies underpinning these newer therapies were conducted in populations considerably younger than the average age of patients presenting with CLL in real-life clinical settings, leading to the underrepresentation of the type of patients most likely to present with CLL. Additionally, in current trials, around 20–30% of participating patients are Binet stage A, and as such not necessarily representative of the majority requiring treatment. This is perhaps unsurprising, as the management of elderly, unfit patients with CLL can be complex, with treatment outcomes often compromised by comorbidities and poor performance status. The advent of newer therapies has led to greater focus on the evaluation of the fitness status of CLL patients, which is essential to enable the appropriate treatment for the individual patient to be better defined. Subsequently, the challenge facing today's practicing physician is how to improve the management of elderly, unfit patients with CLL, in terms of balancing outcomes and quality of life.

Latterly, new therapeutic regimens with reduced toxicity profiles have achieved promising results, and it is hoped that they will modify the paradigm of treatment in elderly, unfit CLL patients. Indeed, the data emerging from trials of these new therapeutic regimens raise the question of whether we may expect better outcomes in this population. This review discusses the issues surrounding this topic, beginning with the current tools used in the evaluation of patient 'fitness', and ways in which these can be improved. The current 'standard of care' for fit patients will be considered, along with advances in the treatment of 'unfit' patients in terms of balancing toxicity profiles and quality of life, with a final focus on the importance of a chemotherapy backbone in the first-line treatment of CLL in this patient population. The issues discussed inevitably lead to the question of whether we should be raising our expectations in the treatment of elderly unfit patients, and in fact, using the newer therapies now available, be aiming for similar outcomes to those achieved in fit patients.

CLL: a disease of the elderly

At diagnosis, 70% of CLL patients are over 65 years old [1], and the median age at diagnosis is 72 years. Over the age of 65, the incidence of new diagnoses reaches 22–30/100,000 per year [1]. Figure 1 represents the percentages of diagnoses within different age groups, highlighting the fact that the disease is most prevalent in people aged over 65 years.

Such patients are often medically less fit, and compared with younger patients are likely to have a greater comorbidity burden, including immunosuppression, renal impairment, and cardiovascular and pulmonary disease. A further major comorbidity occurs where underlying myelodysplasia eventually favors long-lasting cytopenias. There is evidence to suggest that myelodysplasia, and subsequently cytopenia, may occur more frequently in CLL patients who have previously been treated with a combination of purine analogues and alkylating agents [2,3].

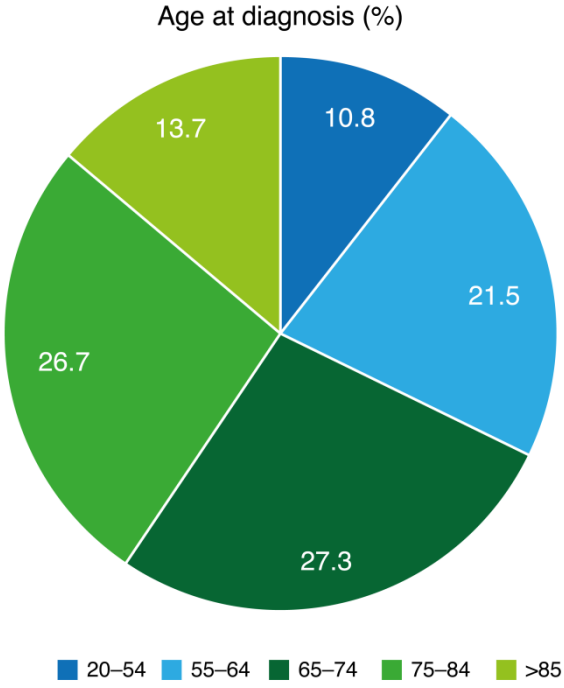

Figure 1: CLL – age at diagnosis. [green segments represent patients over 65 years] [1].

Furthermore, there is evidence to suggest an increased incidence of certain co-morbidities in CLL patients, such as congestive heart failure and chronic pulmonary disease, which supports the concern that these patients may undergo an accelerated aging process as a consequence of CLL, [4–6], potentially exacerbating the comorbidity problem. Although age itself has been shown to be an independent predictor of survival in CLL patients [7,8], a recent study comparing patients younger than 70 years to patients older than 70 years found that karyotype abnormalities and p53 deletions, amongst other parameters, were detected in the same order of magnitude in both populations. These results suggest that whilst co-morbidities become an increasing problem with advancing age, no significant differences exist in the pathophysiology of CLL between younger and elderly patients.

Evaluation of 'fitness' in CLL: the need for a standardized system

That CLL is primarily a disease of the elderly draws attention to the need for a suitable system for assessing patient fitness. As discussed, elderly CLL patients as a generalized population may be more likely to suffer comorbidities, although conversely, there are some elderly patients with a good fitness status, without significant comorbidities, such as renal insufficiency or chronic lung disease, which would be likely to compromise treatment outcomes due to the probable side effects. These different groups of elderly patients may well respond very differently to a given therapy, a fact that highlights an obvious flaw in the traditional approach of using chronological age as the most important factor in determining the treatment approach. Awareness of this has been raised in recent years, particularly with the increased use of the purine analogue fludarabine. Subsequently the importance of assessing a patient's 'biological age', through consideration of the burden of comorbidities and fitness status, in addition to chronological age, is now recognized [9].

Several different scores and indices are used to determine biological age, through the assessment of performance status and comorbidities of patients with CLL, highlighting the need for consensus to be reached. As a result, patient management may vary between institutions according to which measures are used to determine these criteria. Furthermore, clinical trials performed in this population are difficult to compare to one another because the indices used to assess fitness are not standardized, leading to great heterogeneity between trial populations. Current measures used to determine performance status include the Eastern Cooperative Oncology Group [ECOG] performance status [10], and the Karnofski performance scale. Alongside these, the Charlson comorbidity index, as well as the Cumulative Illness Rating Scale [CIRS] [11] are used to assess the burden of comorbidities. When health-related quality of life is the outcome of interest, the CIRS can be a good choice as a measure of comorbidity [12]. Widely used by geriatricians, but less so by oncologists, it assesses the existence of comorbidities in different organ systems in daily clinical practice. The CIRS score can, however, be unreliable, due to the way it rates organ dysfunction and it still requires validation in cohorts of unselected CLL patients representative of CLL in real life [9].

More recently, in order to refine the method of determining the best treatment approach, there has been a focus on 'risk-adaptive approaches' to therapy, which attempt to weigh the potential benefit that a patient may receive from treatment against the negative effects of adverse treatment-related events. Strategies incorporating prognostic factors, together with medical fitness status and other patient characteristics have been proposed. The German Chronic Lymphocytic Leukaemia Study Group [GCLLSG] have used the CIRS score and have proposed their own classification, intended as a simplified means of classifying fitness status, based around FCR [fludarabine, cyclophosphamide, rituximab] tolerability [13]. The GCLLSG score defines patients as:

Go-Go – 'Fit' young, otherwise healthy patients suitable for standard treatment.

Slow-Go – 'Unfit' elderly patients with comorbidities suitable for reduced treatment.

No-Go – Frail patients who are otherwise suitable for supportive care only.

This classification is essentially based on scoring by CIRS, but aims to overcome its shortfalls in these circumstances, as physicians using the CIRS must score comorbidity on a purely subjective basis. For example, whether arterial hypertension requiring medication is scored as '1' or '2' is determined solely at the physician's discretion. Whilst the GCLLSG score represents an advance in this area, it has not been universally adopted. The GCLLSG itself has used the CIRS in all its studies since the CLL8 trial, which began in 2003 [14], and the co-operating European CLL study groups also favor the CIRS-based score, whereas the German CLL registry uses the Charlson score. Latterly, it has been established that some elderly patients otherwise potentially classified as 'Slow-Go' could tolerate more aggressive therapies, and it is believed that this particular group of patients may sometimes receive sub-optimal treatment [14]. As an example, a randomized trial comparing FC [fludarabine, cyclophosphamide] and FCR therapy demonstrated similar response rates and progression-free survival [PFS] between patients under 65 years compared with those

over 65 years, classed as 'fit' according to their CIRS and creatinine clearance scores. Whilst the older patient group tolerated both treatments fairly well, they did, however, suffer a higher incidence of grade 3–4 adverse events [14]. It is noteworthy that these patients had a median CIRS score of 1 [13]. Due to the lack of clinical studies focusing on 'elderly' CLL patients, guidelines for treatment in these patients are underdeveloped. The following section looks at the current standard of care in Go-Go patients, and how this may be applicable to the 'elderly fit', and also considers the recent advances in the treatment of those patients classed as 'elderly unfit'.

Management of young and elderly, fit, 'Go-Go' CLL patients

Most of the recent advances seen in CLL therapy have benefited young, fit patients. Several studies have demonstrated that the purine analogue fludarabine, in combination with other agents, has greatly improved treatment success in such patients, yielding higher response rates and longer PFS than other treatments [15–21]. FCR is currently recommended as the standard first-line regimen for treatment of CLL in 'Go-Go' patients with advanced, active disease [22], and may also be a suitable choice for the elderly fit. In first-line treatment, FCR was associated with a significantly higher complete response rate, median PFS, and overall survival [OS] than FC in treatment-naïve, physically fit patients [aged 30–81 years] with CD20-positive CLL in the CLL8 phase III trial [14].

The situation for those patients who fall within this 'Go-Go' group, but have genetic aberrations such as del[17p] or TP53 mutations, is different. Both of these cytogenetic markers are predictive of poorer outcomes and are used to guide treatment decisions. These particular mutations lead to poor remission rates, PFS and OS with regard to chemotherapy, chemoimmunotherapy and immunomodulators [23]. However, due to a lack of studies in such patients, it is difficult to recommend the best treatment approach, although alemtuzumab, especially in combination with corticosteroids, has been shown to be effective, and could be used as an alternative to FCR [23]. Allogeneic hematopoietic stem cell transplantation [alloSCT] is also recommended in eligible patients once response is achieved [24].

Treatment of elderly unfit 'Slow-Go' patients

Although FCR is described as the 'standard of care' in 'Go-Go' young, fit patients, it is often neither suitable nor beneficial in those patients falling outside this group, such as 'Slow-Go' patients who are elderly and unfit, due to both its toxicity profile and poorer outcomes, as these patients are often unable to tolerate the full six cycles of therapy. Whilst its toxicity is partly dependent on age, there is also a genetic influence, with certain polymorphisms possibly associated with greater toxicity. That such patients are ineligible for FCR is a significant issue, as this group represents the majority of those diagnosed with CLL.

FCR therapy is not suitable for the majority of CLL patients

FCR phase II trials showed that elderly patient subgroups showed significantly lower rates of complete remission, with longstanding cytopenia and infections being the leading cause of early treatment discontinuation [3,19]. Similar results have also been shown by other studies, and a selection are summarized in Table 1. Less toxic first-line treatment options are therefore required, particularly for those patients with comorbidities or high-risk cytogenetic abnormalities for whom fludarabine monotherapy or FCR is inappropriate due to excessive toxicity relative to the remission rates likely to be achieved. This need was further highlighted with the recent publication of a retrospective analysis of 949 patients, which compared the treatment and prognosis of elderly patients [over the age of 70] with younger patients [below the age of 70]. The analysis, which investigated a variety of treatment options, including amongst others alkylating agents, purine analogs and chemoimmunotherapies, demonstrated that, compared with the younger patient group, only a small proportion of elderly patients were able to receive effective treatment as it is currently perceived [25].

Several studies have investigated fludarabine as monotherapy in patients falling outside the 'Go-Go' category. A phase III trial found that in patients with a median age of 70 years, whilst fludarabine yielded higher overall and complete remission rates than chlorambucil, there was no improvement in PFS or OS [26]. These results were similar to the LRF CLL4 phase III trial, which also showed no difference in PFS or OS rates, although this investigated fit patients with a low comorbidity burden [15]. Furthermore, fludarabine was found to be more toxic than chlorambucil in elderly patients [15,26,27].

Alternatives to fludarabine in elderly unfit patients

Following the German CLL5 trial, single-agent treatment with chlorambucil has typically been the first-line treatment of choice for those elderly, frail or comorbid patients without del[17p] who are unable to tolerate fludarabine or FCR, due to its more tolerable toxicity profile [22,26,28]. It is generally viewed as a reasonable treatment option in these patients [28]. The potential of chlorambucil in combination with rituximab has also been investigated in two phase 2 clinical trials [29,30]. One of these trials demonstrated an increase in overall response rate of 16% when compared with the chlorambucil arm of the UK CLL4 study [15,28,31].

Other chemotherapeutic agents in combination with rituximab have been shown to offer feasible front-line treatment in patients ineligible for FCR therapy. Examples include dose-reduced purine analog-based therapies, utilizing low-dose regimens of fludarabine, pentostatin and cyclophosphamide, in combination with immunotherapy. One such combination, 'FCR-lite', consists of reduced-dose fludarabine [20 mg/m^2] and cyclophosphamide [150 mg/m^2] in combination with rituximab, increased to 500 mg/m^2, administered every other week. During the maintenance period, rituximab is administered at the same dose at 3-monthly intervals until relapse. A phase II trial investigating FCR-lite has shown promising results in previously untreated CLL patients [with a median age of 58 years and only 20% in Rai stage III–IV], though patient numbers are low. The median OS has not yet been reached [32,33].

Despite the reduced toxicity profile seen with chlorambucil, the outcomes achieved fall some way behind those seen with FCR. Current trials are investigating alternatives that may be suitable in those patients ineligible for FCR therapy, and several have focused on the alkylating agent bendamustine, either as monotherapy or in combination with rituximab [34–38].

		Treatment outcome		Serious Adverse Events and Toxicities
Trial	**Age [years]**	**CR [%]**	**ORR [%]**	**Percentage of patients unless specified otherwise**
Keating et al., 2005 [19] N=224	FC: 53 [median] FCR: 57 [median] FCR: < 55 FCR: 55–69 FCR: ≥ 70	FC: 35 FCR: 70 [P< 0.05] FCR: 80 FCR: 68 FCR: 47	FC: 88 FCR: 95 FCR: 96 FCR: 96 FCR: 87	Major infections: 2.6% of courses Grade 3/4 events: Neutropenia: 52% of courses Fever and Chills: 1% Hypotension: 1%
Eichhorst et al., 2009 [16] N=183	F+: 71 [median] Clb‡:70 [median]	F: 7 Clb: 0 P=0.011	F: 72 Clb: 51 P=0.003	Grade 3/4 events*: Leukocytopenia: 28+/3‡ Neutropenia: 12+/12‡ Anemia: 15+/27‡ Thrombocytopenia: 15+/20‡
Knauf et al., 2013 [German prospective TLN registry] [35] N=613	FCR: 65 [median] BR: 71 [median]	FCR: 40 BR: 45	FCR: 97 BR: 92	N/A
Leblond et al., 2013 [MaBLe] [38]	Clb-R+: 73 [median] BR‡: 75 [median]	Clb-R: 10 BR: 24 [p=0.033]	Clb-R: 81 BR: 88	Grade 3/4 events: Neutropenia: 34+/32‡ Pneumonia: 2+/7‡

Table 1: Indirect comparisons of fludarabine-based treatment outcomes in studies of patients of different median ages. Results are not directly comparable due to different definitions of complete remission between trials. CR, complete remission; ORR, overall response rate; F, fludarabine; FC, fludarabine + cyclophosphamide; FCR, fludarabine + cyclophosphamide + rituximab; BR, bendamustine + rituximab; Clb, chlorambucil.

*classified by CTC criteria

Bendamustine has a mechanism of action that differs from other alkylating agents [39,40]. As with chlorambucil, its tolerability profile is attractive in those patients who are unable to tolerate fludarabine, however, the current data suggest that this is combined with a better efficacy profile than chlorambucil.

A phase III trial investigating the efficacy of bendamustine versus chlorambucil as first-line therapy demonstrated that bendamustine offered significantly greater efficacy than chlorambucil for most of the measures investigated, resulting in higher OS, complete remission and PFS [36]. These trial data led to US Food and Drug Administration [FDA] approval, and the licensing of bendamustine as monotherapy in Europe. A follow-up analysis at 54 months confirmed the findings, also demonstrating significantly longer OS in those patients who had achieved objective response or complete remission [irrespective of first-line treatment], although OS was not statistically different between treatment arms [37]. These benefits were achieved without a reduction in quality of life versus chlorambucil, with a manageable toxicity profile.

The use of bendamustine as an alternative chemotherapy backbone has been the focus of several recent trials. The Phase II CLL2M trial investigated bendamustine and rituximab [BR] as first-line therapy in 117 patients, 25.6% of whom were aged 70 years or older. An overall response rate of 88% was reported, with a complete remission rate of 23%. In addition, major toxicities were infrequent [41]. First outcome data collected from the German Prospective TLN registry show results in an even more representative population. BR was compared to FCR in patients with a median age of 71 and 65 respectively, and the data show similar response rates to the first-line treatment in both treatment arms. Despite the lower median age of the FCR patients, the overall response rate of the two arms was similar. Furthermore, after age adjustment, there was no difference in PFS and OS with FCR and BR [35]. It should be noted that these findings are descriptive, and not statistically calculated.

The CLL10 trial is comparing BR to FCR in previously untreated, physically fit patients. Interim results [27.9 months] show an advantage to FCR in terms of complete remission rate, PFS and event-free survival. However, in the subset of patients aged over 65 years, more representative of the majority of patients with CLL, the advantage seen with FCR regarding PFS was lost. Furthermore, there was no difference in either OS or overall remission rate between treatment arms [34]. From a safety perspective, FCR-treated patients had significantly more frequent, severe CTC grade 3–5 adverse events throughout the observation period [90.8% vs. 78.5%, p<0.001]. Rates of severe haemotoxicity, severe neutropenia and severe infections, particularly in the elderly, were all significantly greater in the FCR treatment arm [34]. It is noteworthy that the median age of participants in this trial is 62 years, and thus not representative of the mean age at diagnosis; only 21% of the patients were aged 65 years or older, and just 14% were 70 years or older; only a minority represented the 'typical' age of patients with CLL.

The phase IIIb MaBLe trial is currently ongoing, investigating BR versus chlorambucil and rituximab [Clb-R] in first- and second-line patients with a median age of 74 years. Interim analysis results showed 24.1% in the BR arm had confirmed CR, compared with 10.3% in the Clb-R arm, with the authors concluding that, based on these preliminary data, both treatments may represent a viable treatment option for those ineligible for fludarabine regimens [38]. An overview

of treatment outcomes in the German prospective TLN registry and MaBLe trials is shown in Table 2.

Trials investigating the safety and efficacy of new anti-CD20 monoclonal antibodies, such as ofatumumab and obinutuzumab [GA101] in combination with chemotherapeutic agents, are also currently taking place. Updated stage 1 results reported from the CLL11 trial, investigating first-line chemoimmunotherapy in CLL patients with comorbidities, suggested that chlorambucil combined with GA101 [the combination is known as GClb] led to an improvement in PFS compared with chlorambucil alone. Recently reported results from the stage 2 analysis demonstrated statistically significant prolongation of PFS, together with a higher overall response rate for GClb compared with chlorambucil and rituximab [RClb] [42]. Regarding the safety profile, grade 3–5 adverse events [during treatment] were greater with GClb than with RClb [70% vs. 55%]; percentages of infusion-related reaction and neutropenia were 20% vs. 4% and 33% vs. 28% respectively [GClb vs. RClb]. Another phase 3 trial currently underway, RIAltO [NCT01678430], is investigating the use of ofatumumab and bendamustine compared with ofatumumab and chlorambucil, both followed with idelalisib maintenance, in patients ineligible for more intensive combination chemotherapy. The primary completion date of this trial is 2017.

For relapsed patients falling within the 'Go-Go' and 'Slow-Go' groups, with no cytogenetic mutations, first-line therapy can be repeated if the relapse occurs later than 12–24 months after monotherapy or 24–36 months after chemoimmunotherapy [22]. Bendamustine as monotherapy, and in combination with rituximab [BR] have been used as an alternative following relapse with FCR and other therapies, and their use is supported by clinical data [43,44]. Other treatment options for this group include monotherapy with alemtuzumab or ofatumumab.

The results obtained to date from trials investigating bendamustine versus other chemotherapeutic agents suggest that, in patients for whom FCR therapy would be unsuitable, such as many of those patients aged over 70 years, bendamustine should be considered as a more suitable alternative, in combination with a CD20 antibody. The similar efficacy to FCR, together with a reduced toxicity profile and greater tolerability, suggest that for these patients, bendamustine may represent the chemotherapy backbone of choice. In addition, the potential for combination of bendamustine with the immunotherapies currently under development could further improve treatment prospects for these patients, who in fact are the majority. As such, newer chemotherapeutic agents such as bendamustine give clinicians the possibility of raising their expectations of outcomes for their elderly, unfit patients compared with agents such as chlorambucil. Together with future improvements and consensus in classifying and thus identifying these patients, clinicians may be able to better target these newer, less toxic therapies to those who are likely to benefit most from them.

More recently, the advent of "targeted" drugs is offering new options even in patients with several lines of pre-treatment including nucleoside analogs, bendamustine, alkylators, and monoclonal antibodies. There is a debate on the goal of 'chemo-free' treatment in CLL while a series of trials dealing with this issue are still ongoing.

Chemotherapy-free treatment strategies

Chemotherapy-free treatments have recently become the focus of considerable research interest, both as first-line and as second-line or maintenance therapies. These treatments include PI3K inhibitors, monoclonal antibodies against CD20 and CD52, Bcl-2 inhibitors, Bruton's tyrosine kinase [BTK] inhibitors and immunomodulatory agents. The following section briefly summarizes some of the interesting developments in this area.

		Treatment outcome		Serious adverse events and toxicities
Trial	**Median age [years]**	**CR [%]**	**ORR [%]**	
Knauf et al., 2014 [German prospective TLN registry] [35]	FCR: 65 BR: 71	FCR: 40 BR: 45	FCR: 97 BR: 92	N/A
Leblond et al., 2013 [MaBLe] [38]	Clb-R: 73 BR: 75	Clb-R: 10 BR: 24 [p=0.033]	Clb-R: 81 BR: 88	Grade 3/4 events: Neutropenia: 34+/32‡ Pneumonia: 2+/7‡

Table 2: Early trial data indirectly comparing treatment outcomes in patients treated with BR, versus FCR and Clb-R. Results are not directly comparable due to different definitions of complete remission between trials. CR, complete remission; ORR, overall response rate; FCR, fludarabine + cyclophosphamide + rituximab; BR, bendamustine + rituximab; Clb, chlorambucil

In 2007, results of a phase III trial comparing the CD52 antibody alemtuzumab with chlorambucil as first-line therapy for CLL were published. The primary endpoint, PFS, was improved with respect to chlorambucil, as was time to alternative treatment, overall response rate and complete remission. OS data were not reported [45]. However, its toxicity profile has been less favorable, meaning it is infrequently used in older patients. Its use is restricted to 'high risk' patients with TP53 mutations or 17p, as it has been shown to be active in such patients [46–48].

The PI3Kδ inhibitor idelalisib has recently been investigated in combination with rituximab, in previously treated patients ineligible for chemotherapy, including those with adverse genetic features. Compared with patients treated with rituximab alone, idelalisib plus rituximab demonstrated a statistically significant improvement in PFS, overall response rate, lymph-node response and OS [49]. Although there have been concerns that idelalisib may cause liver damage [49], the safety profile of idelalisib plus rituximab was acceptable, and the favorable results led to a recommendation by the Data Monitoring Committee to end the trial early. A phase III trial investigating idelalisib plus BR versus BR alone in previously treated patients is also currently underway [NCT01569295].

The B-cell lymphoma 2 [Bcl-2] inhibitor ABT-199, used as monotherapy in the treatment of relapsed/refractory CLL, has also shown promising preliminary results. A phase I study that includes del[17]p and F-refractory disease, and a phase II monotherapy study in patients with del[17p] CLL, are both underway [50]. Regarding safety, it has been suggested that ABT199 treatment might induce a cytokine release syndrome [51]. ABT-199 is also associated with tumor-lysis syndrome [52]

The BTK inhibitor ibrutinib [PCI-32765] has been investigated as monotherapy in a phase I study and a phase Ib/II continuous-dosing study in both treatment-naïve and relapsed or refractorypatients. The

study is ongoing, and the interim results suggest long-term safety, tolerability and duration of response in treatment-naïve or relapsed or refractory CLL patients [53], although it has previously been suggested that ibrutinib may contribute to bleeding disorders. Ibrutinib gained FDA approval for use in previously treated patients with CLL in February, 2014. In October 2014, the EMA granted approval of ibrutinib for use in adult patients with CLL who have received at least one prior therapy, or as first line therapy in patients who have a 17p deletion or TP53 mutation who are also unsuitable for chemo immunotherapy.

The use of lenalidomide, an immunomodulatory drug is under investigation in CLL, both as first-line therapy and also in patients with relapsed/refractory disease. A recent phase II study assessing lenalidomide in combination with rituximab showed promising results in elderly patients. A response rate of 78%, including 20% complete response, was observed among patients with a median age of 70 [54]. However, drug development was subsequently interrupted in 2013 when the FDA halted a clinical trial of lenalidomide vs. chlorambucil due to significant safety concerns, citing a higher risk of death in the lenalidomide arm [55]

Despite the results outlined, the data currently available suggest that the likelihood of achieving complete molecular remissions remains far greater with a chemotherapy backbone, but these results hold promise for the treatment of patients for whom chemotherapy is unsuitable. However, as outlined above, the toxicity of some novel small molecules and antibodies may still be an issue that precludes their use in elderly, unfit patients. Further investigation is needed before such treatments are widely recommended for the treatment of elderly, unfit patients.

Conclusions

The management of elderly patients with CLL is complex, not least because the best method for assessing and measuring patient fitness status has not yet been adequately defined in CLL, or universally agreed upon [9]. We suggest that the advent of new chemotherapeutic and chemotherapy-free treatments has highlighted the need for a more stringent classification of elderly patients, for example the 'elderly fit' and 'elderly unfit', in order to ensure each patient receives the most appropriate treatment. Refinement of a system such as the GCLLSG grouping, and the universal implementation of its use, would help to ensure that all those ineligible for FCR therapy receive optimal treatment. However, any such new method of measuring fitness must be simple and easy to use in clinical practice and will require large and comprehensive validation.

Despite the historically poor outlook for the majority of patients with CLL, classed as 'unfit' and unable to tolerate FCR therapy, recent advances have led to improvements in their treatment and the prospect of better outcomes more in line with those in fitter, mostly younger patients. Chemotherapy-free treatments show promise for those patients unable to tolerate chemotherapy, but the best treatment for the majority of patients, at least today, remains based around a chemotherapy backbone. For example, treatment with bendamustine as a frontline therapy, both alone and in combination, has been key in the improvement of treatment options and outcomes also in 'unfit' patients, due to a better tolerability profile than that seen with FCR, but together with similar efficacy. The advent of newer regimens, that provide similar efficacy versus traditional regimens, together with better tolerability profiles in elderly unfit patients, leads to the question of whether we should be raising our expectations of treatment in elderly, unfit patients, and aiming for similar outcomes to those expected in fit patients.

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